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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/749,522	01/02/2004	Beka Solomon	SOLOMON=2B.2	9533

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EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/749,522	SOLOMON ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 25-34* is/are pending in the application.

4a) Of the above claim(s) *1-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-11 and 25-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The response filed on 13 April 2009 has been received and entered in full. Claims 1-11 and 25-34 are pending in the instant application.

Claims 1-6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicants timely traversed the restriction (election) requirement in the reply filed on 13 June 2006.

This application contains claims 1-6 drawn to an invention nonelected with traverse in the reply filed on 13 June 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 7-11 and 25-34 are under examination in the instant office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7-11 and 25-34 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Solomon et al. (Proc Natl Acad Sci USA, April 1997; 94:4109-4112 as listed on Applicant's IDS) and Hanan & Solomon (Amyloid: Int J Exp Clin Invest, 1996; 3:130-133, listed on IDS), both as evidenced by Frenkel et al. (J Neuroimmunol, August 1998; 88: 85-90, listed on IDS), and both in view of US Patent No. 5,622,699 to Ruoslahti et al., issued 22 April 1997, filed 11 September 1995 and US Patent No. 5,846,533 to Prusiner et al., issued 8 December 1998, filed 13 September 1996 (listed on IDS).

The claims are drawn to a pharmaceutical composition comprising a filamentous bacteriophage, wherein said filamentous bacteriophage consists of a filamentous bacteriophage that displays an antibody or epitope binding fragment thereof, wherein said antibody and epitope binding fragment thereof bind to an epitope of β-amyloid so as to inhibit aggregation of β-amyloid in a subject and/or to cause disaggregation of a β-amyloid aggregate in a subject, wherein said filamentous bacteriophage displaying said antibody or epitope binding fragment is an active ingredient of the composition and the composition further comprises a pharmaceutically acceptable carrier (claims 7-11). The claims are also directed to a composition comprising said bacteriophage displaying said antibody or epitope binding fragment and a carrier (claims 25-29). The claims are further drawn to a filamentous bacteriophage that displays an antibody or epitope binding fragment thereof as described above (claims 30-34). Additional claim limitations include: wherein said epitope of β-amyloid comprises SEQ ID NO: 1 (claims 8, 26, and 31), wherein said antibody or binding fragment is displayed on said bacteriophage via coat glycoprotein VIII (claims 9, 27, and 32), wherein said epitope is contained in a peptide selected from the group consisting of SEQ ID NOs: 7, 8, 21 and 22 (claims 10, 28, and 33), and wherein said β-amyloid is selected from the group consisting of A β39, A β40, A β41, Aβ42, and A β43 (claims 11, 29, and 34).

The teachings of Solomon et al. and Hanan & Solomon are cumulative. Both references teach the inhibition and disaggregation of β-amyloid peptide by monoclonal antibodies. The monoclonal antibodies found to be significantly effective in interfering with the aggregation of β-amyloid *in vitro* are 6C6 and 10D5, both of which recognize an

epitope within Aβ1-16 (see Figure 1 of each reference). Solomon (1997) also demonstrates that the 6C6 mAb (monoclonal antibody) was effective at inhibiting the neurotoxic effects of fibrillar β-amyloid on PC12 cells in culture (see Figure 4, p. 4111). For these experiments, the antibodies were added in a composition comprising phosphate-buffered saline (PBS) (see p. 4110, 1st paragraph), as in the claimed limitation of a pharmaceutically acceptable carrier or simply, a carrier. Although the specific anti-aggregating epitope that these antibodies recognize is not specifically recited by the authors, subsequent work from this group established that the N-terminal EFRH sequence, which is the instantly claimed SEQ ID NO: 1, is residues 3- 6 of β-amyloid and represents the sequential epitope of mAbs 6C6 and 10D5 (see Frenkel et al., 1998), as in claims 8, 26, and 31. The EFRH sequence is also contained within each of the amino acid sequences of SEQ ID NOs: 7, 8, 21, and 22, as in claims 10, 28, and 33. Solomon et al. (1997) notes that Alzheimer's disease-associated plaques are predominantly comprised of a 40-to 42-mer β-amyloid peptide (see p. 4109, 1st paragraph), as in claims 11, 29, and 34. Solomon et al. thus suggests that high-affinity, site-directed mAbs (or compounds that may mimic their biological activities as genetically engineered small antibodies or peptide mimetics), which trigger reversal of the pathological aggregation of β-amyloid to its nontoxic components, may be used in the development of therapeutic active molecules for the treatment of such diseases as Alzheimer's disease and prion diseases (see p. 4112).

Neither Solomon et al. nor Hanan & Solomon teach compositions comprising filamentous bacteriophage which displays an antibody or epitope binding fragment

thereof. However, the Ruoslahti et al. patent teaches an *in vivo* panning method that comprises screening a phage peptide display library in mice and identifying specific peptides that selectively home to brain or to kidney. The patent teaches that phage libraries that display protein receptor molecules, including an antibody or an antigen binding fragment of an antibody such an Fv, Fd or Fab fragment; can be used to practice the invention (col. 4, lines 21-37). Thus, the reference teaches that an antibody or epitope binding fragment thereof can be displayed on a bacteriophage for *in vivo* administration.

None of the above cited references teaches displaying the antibody or epitope binding fragment thereof on the bacteriophage via coat glycoprotein VIII. However, the Prusiner et al. patent teaches methodologies for producing a variety of different prion protein antibodies for use in neutralization or purification of prion proteins or for *in vivo* use (see column 4, lines 61-67). For this purpose, Prusiner et al. teach genetically engineered phages which express a specific binding protein of an antibody on their surfaces (see column 5, lines 3-5). The desired antibody, such as an intact antibody or Fab or Fv antibody fragment (see column 23, lines 31-32), displayed on the surface of a filamentous phage (e.g., M13, fl, fd, and equivalent filamentous phages) is anchored via a membrane anchor domain found in the coat proteins encoded by gene III or gene VIII (i.e., cpIII or cpVIII coat proteins) (see column 24, line 38 through column 25, line 4, and column 26, lines 35-41), as in claims 9, 27, and 32.

Upon reading the disclosure of the Solomon reference and the Hanan & Solomon reference, the skilled artisan would have recognized the desirability of developing

compositions comprising Aβ anti-aggregating antibodies. Furthermore, the Ruoslahti et al. patent teaches that antibodies or epitope binding fragments thereof can be displayed by a bacteriophage for *in vivo* use. Thus, as evidenced by the prior art, the skilled artisan would have known that developing alternative antibody compositions would be desirable. Furthermore, it would have been reasonable to predict that the anti-aggregating antibodies or epitope binding fragments thereof of the Solomon et al. and the Hanan & Solomon references could be successfully displayed by a bacteriophage via coat glycoprotein VIII as taught by Ruoslahti et al. and Prusiner et al. Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to improve the antibodies or epitope binding fragments as disclosed by Ruoslahti et al. and Prusiner et al. to yield predictable results. This is because the artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. The skilled artisan would have been motivated to display the antibodies of Hanan & Solomon because Ruoslaht teaches that an advantage of the phage display methods is that after *in vivo* administration, the phage can be recovered and quantified to reveal information about the molecule that it displayed (see Example 1). Ruoslahti teaches that an advantage of using the phage display technology is that the molecules that have already been identified as homing to a specific target (in this case, the brain) can be displayed on phage for binding composition studies (see Example 2 "Characterization of peptides that home to a specific organ", especially beginning at col.18, line 60, "C. Peptide homing is specific"). The skilled artisan could thus adapt the phage display technology with the antibody of Solomon and Hanan for

various screening methods that test binding of the antibody, e.g. for testing the therapeutic efficacy of the antibody. For example, quantifying the amount of phage in brain tissue to reveal the amount of antibody binding after *in vivo* administration of antibody displayed on phage would be an alternative to other antibody binding assays for testing antibody efficacy. The skilled artisan would have had a reasonable expectation of success in displaying the antibodies on a phage because Ruoslahti et al. and Prusiner et al. support such a reasonable expectation of success (entire documents).

In the reply filed on 13 April 2009, applicants assert that the examiner has not explained where in the disclosures of Ruoslahti and Prusiner is a suggestion that antibodies can be improved by displaying them on a phage. Applicants assert that Ruoslahti teaches no diagnostic use for a filamentous phage displaying an antibody. Applicants assert that the word "diagnostic" appears only twice in the Ruoslahti parent and in both cases, Ruoslahti is referring to the molecule that is obtained using the phage library. Applicants assert that Ruoslahti's definition of "molecule" does not include the presence of phage and that the phage is used to identify the molecule. Applicants assert that once the molecule is identified, it is the molecule that is used as the organ homing molecule, not the phage displaying the molecule. Applicants assert that there is absolutely nothing in Ruoslahti that the examiner can point to which suggests use of a phage displayed antibody other than as part of a screening process. Applicants concede that the examiner is correct that Ruoslahti uses the bacteriophage

to identify molecules that home to the brain but assert that the examiner is totally wrong in stating that this is a "diagnostic use." Applicants assert that this is nothing more than a screen. Applicants assert that the organ homing antibodies that are found using the process are then synthesized or otherwise produced and then used per se for diagnostic purposes. Applicants assert that the method of Ruoslahti is not a diagnostic use and is not a therapeutic use but is a use to screen for antibodies (i.e., to find useful antibodies). Applicants allege that there is absolutely no reason whatsoever why one of ordinary skill in the art would use phage display technology with an antibody that has already been identified and selected. Applicants concede that one of ordinary skill in the art would know how to put such an antibody on the pVIII coat protein of a phage but this is insufficient to establish obviousness. Applicants assert that there must be some reason for one of ordinary skill in the art to do so and that none of the references of record or "common sense" provide a reason.

Applicants' arguments have been fully considered and are not found persuasive. It appears that applicants and the examiner are aware of different definitions of the term "diagnostic." "Diagnosis" is defined as "the identification of the nature of anything, either by process of elimination or other analytical methods. Diagnosis is used in many different disciplines, with slightly different implementations on the application of logic and experience to determine the cause and effect relationships." (Wikipedia definition, http://en.wikipedia.org/wiki/Diagnosis, retrieved on 14 July 2009). Thus, contrary to applicants' allegations, according to one published definition of "diagnosis," Ruoslahti's method of using antibodies displayed on phage for "screening" purposes is indeed a

"diagnostic use." Ruoslahti method of identifying antibodies as homing to the brain can be thought of as identifying the nature of the antibody, which is indeed embraced by the definition of "diagnosis." Applicants' apparent, and more rigid, view that a "diagnostic use" only includes diagnosis of disease is inaccurate and thus, Ruoslahti indeed teaches displaying an antibody on phage and this is indeed a diagnostic use. Ruoslahti's screening methods are enough to suggest to the skilled artisan that an antibody can be displayed on phage for *in vivo* administration as the examiner has repeatedly set forth on the record. In response to applicants' argument that there is no suggestion to combine the references, it is noted that KSR forecloses the argument that a specific teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>). The teaching, suggestion, or motivation rationale is now one of a number of rationales to support a finding of obviousness.

Regardless, contrary to applicants' allegations, Ruoslahti provides a motivation to support the instant finding of obviousness. Ruoslaht teaches that an advantage of the phage display methods is that after *in vivo* administration, the phage can be recovered and quantified to reveal information about the molecule that it displayed (see Example 1). Ruoslahti also teaches that an advantage of using the phage display technology is that the molecules that have already been identified as homing to a specific target (in this case, the brain) can be displayed on phage for binding composition studies (see

Example 2 "Characterization of peptides that home to a specific organ", especially beginning at col.18, line 60, "C. Peptide homing is specific"). Here, Ruoslahti teaches a reason why one of skill in the art would use phage display technology with **molecules that have already been identified and selected**. The skilled artisan could thus adapt the phage display technology with the antibody of Solomon and Hanan for various screening methods that test binding of the antibody, e.g. for testing the therapeutic efficacy of the antibody, etc. For example, quantifying the amount of phage in brain tissue to reveal the amount of antibody binding in the brain after *in vivo* administration would be an alternative to other antibody binding assays that measure binding in the brain.

Regardless, as stated previously, the instant claims are directed to compositions and are not drawn to methods of diagnosis or treatment. Ruoslahti teaches a composition comprising an antibody or epitope binding fragment displayed on a bacteriophage for diagnostic use to identify molecules that home to the brain. Given that the antibodies of Hanan and Solomon bind to Aβ, a peptide that is expressed in the brain, it would have been reasonable to predict that a composition comprising such an antibody or epitope binding fragment thereof displayed on a bacteriophage would be useful in screening methods adapted from Ruoslahti. Further, applicants are reminded that the recitation of "a pharmaceutical composition" in claims 7-11 has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not

depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478,481 (CCPA 1951). Moreover, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. Given that Ruoslahti explicitly teaches an advantage of displaying an antibody or epitope binding fragment thereof on a bacteriophage for *in vivo* use (i.e., a screening use), the patent teaches an advantage of displaying an antibody, such as those taught by Solomon et al. and/or Hanan & Solomon, on a bacteriophage. Prusiner et al. provides specific teachings of how such an antibody may be displayed on a filamentous bacteriophage, i.e. via coat glycoprotein VIII. Additionally, it is again noted that a composition taught by the combination of the instant prior art references is not incompatible with a therapeutic intent.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

Gregory S. Emch
Patent Examiner
Art Unit 1649
15 July 2009

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
July 16, 2009